The Regulation of MicroRNAs by Brahma-Related Gene 1 in Smooth Muscle Cells

Meng Chen and Paul Herring
Department of Cellular and Integrative Physiology, IU School of Medicine

MicroRNAs (miRs) regulate the phenotypic switch of smooth muscle cells (SMCs) that occurs under several pathological conditions such as atherosclerosis. However, little is known about the transcriptional and epigenetic regulation of miR expression in SMCs. To identify miRs that are regulated by the Brahma-related gene 1 (Brg1)-containing SWI/SNF chromatin remodeling complex we performed a microRNA array screen of RNA isolated from colonic SMCs of mice harboring a smooth muscle-specific knockout of Brg1. Quantitative RT-PCR confirmed changes in expression of several miRs, including miRs-143/145 and miR-133. Expression of dominant negative Brg1 in wild-type SMCs led to decreased expression of miRs-143/145 but not miR-133. The dominant negative Brg1 also blocked the myocardin-mediated induction of miRs-143/145 in 10T1/2 cells. Knockdown of SRF or myocardin decreased expression of miRs-143/145 in SMCs, whereas miR-133 expression was only repressed following SRF knockdown. In Brg1-null SW13 cells, miRs-143/145 but not miR-133 were dramatically induced by myocardin only in the presence of Brg1. Chromatin immunoprecipitation assays revealed that Brg1 is important for myocardin-mediated SRF binding to the miRs-143/145 promoter. Together these data show that Brg1-dependent chromatin remodeling regulates the expression of miRs-143/145 and miR-133 through distinct pathways in SMCs. This implies that chromatin remodeling complexes modulate smooth muscle phenotypes and functions not only through protein coding genes but also non-coding genes.

Mentor: Paul Herring, Department of Cellular and Integrative Physiology, IU School of Medicine, IUPUI